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Neurosci Lett 1996 Aug 9;213(3):205-8

Immunofluorescence analysis of antisense oligodeoxynucleotide-mediated 'knock-down' of the mouse delta opioid receptor in vitro and in vivo.

Lai J, Riedl M, Stone LS, Arvidsson U, Bilsky EJ, Wilcox GL, Elde R, Porreca F

Department of Pharmacology, University of Arizona Health Sciences Center, Tucson 85724, USA. lai@aruba.ccit.arizona.edu

We have previously used antisense oligodeoxynucleotides (ODN) to the cloned delta opioid receptor (DOR) to inhibit the antinociceptive response to spinally administered delta opioid receptor selective agonists in mice. Here we have examined the effect of DOR antisense ODN treatment on the level of DOR expressed in NG 108-15 cells and the spinal cord, through immuno-fluorescence microscopy, to determine the efficiency and selectivity of the antisense ODN-mediated "knock-down' of the DOR in these tissues. Antisense ODN, but not mismatch control, treatment resulted in a significant reduction in DOR immunoreactivity (-ir) in NG 108-15 cells and spinal cord. Thus, the inhibition of antinociceptive response to intrathecal delta selective agonists by DOR antisense ODN correlates with the loss of DOR-ir in the superficial layers of the dorsal horn of the spinal cord.

PMID: 8873150, UI: 97026981

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J Pharmacol Exp Ther 1996 Apr;277(1):491-501

Characterization of antinociception to opioid receptor selective agonists after antisense oligodeoxynucleotide-mediated "knock-down" of opioid receptor in vivo.

Bilsky EJ, Bernstein RN, Hruby VJ, Rothman RB, Lai J, Porreca F

Department of Pharmacology, University of Arizona Health Sciences Center, Tucson, USA.

Pharmacological studies in vivo and in vitro have suggested the existence of subtypes of the delta opioid receptor termed delta1 and delta2 (delta1 and delta2). The hypothesis of subtypes of delta receptors was further explored by assessing the effects of administration of antisense or mismatch oligodeoxynucleotides (ODN) in vivo to the cloned DOR, or to a conserved region of the cloned opioid receptors, on the antinociceptive responses elicited by selective mu, ku and delta opioid receptor agonists in mice. Additionally, the density of opioid delta receptors in brain after delta opioid receptor (DOR) ODN treatment was investigated. Repeated twice daily intracerebroventricular (i.c.v.) administration of DOR antisense, but not mismatch, ODN, produced a dose- and time-related blockade of i.c.v. [D-Ala2, Glu4]deltorphin (delta2 agonist), but not [D-Pen2, D-Pen5]enkephalin (delta1 agonist), antinociception. The antinociceptive responses to selective mu and kappa opioid agonists were unaffected by DOR antisense or mismatch ODN treatments. The antinociceptive effect of an A90 dose of [D-Ala2, Glu4]deltorphin was significantly reduced by the third day of DOR antisense ODN administration and persisted over a treatment period of 6 days with recovery by the third posttreatment day. Saturation studies in mouse whole brain preparations with the selective delta-radioligand [3H]naltrindole showed that DOR antisense, but not mismatch, ODN treatment produced a significant time-related reduction in Bmax values of approximately 30 to 40% by day 6, without changing the Kd value. The reduction in DOR density was reversible and returned to control levels within 3 days after cessation of antisense ODN treatment. The i.c.v. administration of an antisense, but not mismatch, ODN directed to a conserved region of the cloned opioid receptors, termed common opioid receptor antisense ODN, inhibited the antinociceptive effects of i.c.v. mu, kappa and delta agonists, including [D-Pen2, D-Pen5]enkephalin. These data further support the hypothesis of subtypes of opioid delta receptors.

PMID: 8613959, UI: 96185112

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Regul Pept 1995 Oct 20;59(2):163-70

Antisense oligonucleotide inhibition of tryptophan hydroxylase activity in mouse brain.

McCarthy MM, Nielsen DA, Goldman D

Department of Physiology, University of Maryland School of Medicine, Baltimore, USA.

To examine in vivo effectiveness of antisense oligonucleotides against tryptophan hydroxylase (TPH) mRNA, adult male swiss-NIH mice were implanted with in-dwelling cannula into the 4th ventricle and after recovery infused with either antisense oligonucleotide to TPH, scrambled control oligo or saline vehicle for four consecutive days. An additional group of animals bearing cannula were injected a single time i.p. with the TPH inhibitor para-chlorophenylalanine (PCPA; 300 mg/kg). All animals were sacrificed on the afternoon of the 4th day of treatment. TPH activity was measured by enzymatic assay and HPLC quantification of end-product synthesis. There was a significant decrease (> 50%) in TPH activity in both the PCPA-treated and antisense-oligo infused animals compared to either scrambled-oligo or saline-infused subjects (ANOVA; $P < 0.05$). There was no difference between saline and scrambled oligo-infusion. In a separate group of animals treated in the same way, behavioral tests were conducted on the afternoon of the 4th day. Two tests of anxiety, the hole-board apparatus and the elevated plus-maze, indicated some significant effects of PCPA treatment and/or antisense oligo-infusion but confounding effects due to alterations in locomotion could not be ruled out. However, tests on a rotorod apparatus indicated that antisense oligo-infused animals retained good balance and coordination in that their performance significantly improved on the second test, as did that of scrambled-oligo infused animals. In contrast, PCPA-treated animals did not improve, suggesting that locomotor performance had been impaired. These data support the notion that antisense oligo blockade may offer advantages over pharmacological manipulations of enzyme activity.

PMID: 8584751, UI: 96131712

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J Pharmacol Exp Ther 1995 Apr;273(1):359-66

SNC 80, a selective, nonpeptidic and systemically active opioid delta agonist.

Bilsky EJ, Calderon SN, Wang T, Bernstein RN, Davis P, Hruby VJ, McNutt RW, Rothman RB, Rice KC, Porreca F

Department of Pharmacology, University of Arizona, Tucson, USA.

The present study has investigated the pharmacology of SNC 80, a nonpeptidic ligand proposed to be a selective delta agonist in vitro and in vivo. SNC 80 was potent in producing inhibition of electrically induced contractions of mouse vas deferens, but not in inhibiting contractions of the guinea pig isolated ileum (IC50 values of 2.73 nM and 5457 nM, respectively). The delta selective antagonist ICI 174,864 (1 microM) and the mu selective antagonist CTAP (1 microM) produced 236- and 1.9-fold increases, respectively, in the SNC 80 IC50 value in the mouse vas deferens. SNC 80 preferentially competed against sites labeled by [3H]naltrindole (delta receptors) rather than against those labeled by [3H]DAMGO (mu receptors) or [3H]U69, 593 kappa receptors) in mouse whole-brain assays. The ratios of the calculated Ki values for SNC 80 at mu/delta and kappa/delta sites were 495- and 248-fold, respectively, which indicates a significant degree of delta selectivity for this compound in radioligand binding assays. SNC 80 produced dose- and time-related antinociception in the mouse warm-water tail-flick test after i.c.v., i.th. and i.p. administration. The calculated A50 values (and 95% C.I.) for SNC 80 administered i.c.v., i.th. and i.p. were 104.9 (63.7-172.7) nmol, 69 (51.8-92.1) nmol and 57 (44.5-73.1) mg/kg, respectively. The i.c.v. administration of SNC 80 also produced dose- and time-related antinociception in the hot-plate test, with a calculated A50 value (and 95% C.I.) of 91.9 (60.3-140.0) nmol.

PMID: 7714789, UI: 95230563

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Eur J Pharmacol 1994 Jun 2;258(1-2):R1-3

Antisense oligodeoxynucleotide to a delta-opioid receptor selectively blocks the spinal antinociception induced by delta-, but not mu- or kappa-opioid receptor agonists in the mouse.

Tseng LF, Collins KA, Kampine JP

Department of Anesthesiology, Medical College of Wisconsin, Milwaukee 53226.

An antisense oligodeoxynucleotide (A-oligo) to delta-opioid receptor mRNA was utilized to block the expression of mouse delta-opioid receptor in the spinal cord of male ICR mice. Intrathecal treatment with A-oligo (1.6-163 pmol) dose-dependently attenuated the antinociception induced by i.t. administered DPDPE ([D-Pen2,5]enkephalin) or [D-Ala2]deltorphin II, delta-opioid receptor agonist, without affecting the antinociception induced by DAMGO ([D-Ala2-MePhe4,Gly(ol)5]enkephalin) or U50,488H, respective mu- or kappa-opioid receptor agonists. Scrambled sense oligodeoxynucleotide (163 pmol) was ineffective against the tail-flick inhibition induced by DPDPE,[D-Ala2]deltorphin, DAMGO or U50,488H. The studies confirm previous pharmacological studies at the molecular level indicating a distinct delta-opioid receptor for antinociception in the spinal cord.

PMID: 7925585, UI: 95010281

Brain Res 1994 Feb 14;636(2):209-20

Intracerebral administration of antisense oligodeoxynucleotides to GAD65 and GAD67 mRNAs modulate reproductive behavior in the female rat.

McCarthy MM, Masters DB, Rimvall K, Schwartz-Giblin S, Pfaff DW

Rockefeller University, Laboratory of Neurobiology and Behavior, New York, NY 10028.

Increased GABA activity in the medial hypothalamus (HYP) and midbrain central gray (MCG), but not the preoptic area (POA), facilitates sexual receptivity in the female rat [40]. In the current experiments, ovariectomized females were chronically treated with estrogen (via silastic capsules) to maintain a continuously high level of lordosis response. Administration of crystalline antisense oligodeoxynucleotide to the GABA synthetic enzyme, GAD67, into the HYP and MCG significantly and reversibly reduced lordosis response for 1-2 days, but did not inhibit lordosis when administered into the POA. Administration of a control oligonucleotide, consisting of the same nucleotide bases but in a scrambled sequence, did not significantly modulate behavior when infused into any brain areas. When oligodeoxynucleotide antisense to GAD67 was suspended in oil and then infused into the HYP or MCG it was more effective and resulted in less inter-animal variability. Subsequent experiments involving infusions into the MCG compared the effectiveness of antisense oligonucleotides to the two different forms of GAD, known as GAD65 and GAD67. Oligodeoxynucleotides antisense to the mRNA for either gene were effective at reducing lordosis behavior but with a different time course. Oligonucleotide antisense to GAD67 significantly reduced behavior within 24 h of infusion and there was full recovery by 4 days post-infusion. GAD65 antisense oligonucleotide did not significantly reduce behavior until 48 h post infusion and animals did not fully recover to pretest levels of lordosis until 5 days post-infusion. When antisense oligonucleotide for the two genes was administered simultaneously, the inhibition of lordosis was maximal at 24 h and stayed depressed for 4 days. There did not appear to be an additive effect of the two different antisense oligonucleotides when administered together. Tissue GABA levels in HYP and MCG of individual rats assayed by HPLC were no longer correlated with lordosis score after antisense oligonucleotide infusion but were after infusions of scrambled control oligos. Immunoblotting for the two forms of GAD revealed that GAD67 antisense oligonucleotide infusion led to significant decreases in both GAD67 and GAD65 protein levels as compared to infusions of scrambled control oligo. In addition, the levels of a neuronal marker, neuron-specific enolase, also decreased (although nonsignificantly) suggesting either a temporary shutdown of protein synthesis or a degeneration of GABAergic neurons after GAD67 antisense oligonucleotide infusion.

PMID: 8012804, UI: 94282571

Life Sci 1994;55(2):PL37-43

Selective inhibition of [D-Ala2, Glu4]deltorphin antinociception by supraspinal, but not spinal, administration of an antisense oligodeoxynucleotide to an opioid delta receptor.

Bilsky EJ, Bernstein RN, Pasternak GW, Hruby VJ, Patel D, Porreca F, Lai J

Department of Pharmacology, University of Arizona Health Sciences Center, Tucson 85724.

Evidence in vivo has suggested the existence of subtypes of the delta opioid receptor (DOR), which have been termed delta 1 and delta 2. These proposed DOR subtypes are thought to be activated by [D-Pen2, D-Pen5]enkephalin (DPDPE, delta 1) and [D-Ala2, Glu4]deltorphin (delta 2). Recent work in which an antisense oligodeoxynucleotide (oligo) to a cloned DOR was administered by the intrathecal (i.th.) route has demonstrated a reduction in the antinociceptive actions of both i.th. DPDPE and [D-Ala2, Glu4]deltorphin, but not of [D-Ala2, NMPhe4, Gly-ol]enkephalin (DAMGO, mu agonist) in mice. The present investigation has extended these observations by administering the same DOR antisense oligo sequence by the intracerebroventricular (i.c.v.) route and evaluating the antinociceptive actions of i.c.v. agonists selective for delta, mu and kappa receptors. I.th. treatment with DOR antisense oligo, but not mismatch oligo, significantly inhibited the antinociceptive actions of both i.th. DPDPE and [D-Ala2, Glu4]deltorphin but not of i.th. DAMGO or U69,593 (kappa agonist), confirming previous data. In contrast, i.c.v. DOR antisense oligo, but not mismatch oligo, selectively inhibited the antinociceptive response to i.c.v. [D-Ala2, Glu4]deltorphin without altering the antinociceptive actions of i.c.v. DPDPE, DAMGO or U69,593. The data suggest that the cloned DOR corresponds to that pharmacologically classified as delta 2 and further, suggest that this delta receptor subtype may play a major role in eliciting spinal delta-mediated antinociception.

PMID: 8015351, UI: 94285706

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Neuroreport 1994 May 9;5(9):1049-52

Treatment with antisense oligodeoxynucleotide to the opioid delta receptor selectively inhibits delta 2-agonist antinociception.

Lai J, Bilsky EJ, Rothman RB, Porreca F

Department of Pharmacology, University of Arizona Health Science Center, Tucson 85724.

Using approaches emphasizing differential antagonism of receptor selective agonists and cross-tolerance paradigms, evidence in vivo has suggested the existence of subtypes of opioid delta receptors, which have been termed delta 1 and delta 2. Recent work has elucidated the structure of an opioid delta receptor. The present investigation attempted to continue to test the hypothesis of subtypes of delta receptors and to correlate the cloned delta receptor with the existing pharmacological classification. Synthetic oligodeoxynucleotides (oligos) complementary to the 5' end of the cloned delta receptor coding region (antisense) or its corresponding sequence (sense) were given by intracerebroventricular (i.c.v.) administration to mice, twice-daily for 3 days and antinociceptive responses to selective agonists at putative delta 1 and delta 2 receptors were subsequently determined. Treatment with antisense, but not sense, oligo significantly inhibited the response to [D-Ala2,Glu4]deltorphin (delta 2 agonist), but not to [D-Pen2,D-Pen5]enkephalin (DPDPE, delta 1 agonist). Further, subsequent administration of DPDPE elicited a full antinociceptive response in the same antisense oligo treated mice which did not show a significant response to [D-Ala2,Glu4]deltorphin while antisense oligo treated mice which responded to DPDPE did not show antinociception when tested subsequently with [D-Ala2,Glu4]deltorphin. The data suggest that the cloned delta receptor corresponds to that pharmacologically classified as delta 2 and continue to support the concept of subtypes of opioid delta receptors.

PMID: 8080957, UI: 94362183

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Eur J Pharmacol 1993 May 19;236(2):339-40

C-fos antisense in the nucleus accumbens blocks the locomotor stimulant action of cocaine.

Heilig M, Engel JA, Soderpalm B

Department of Psychiatry and Neurochemistry, University of Goteborg, Molndal, Sweden.

Systemic cocaine induces c-fos expression in rat striatum. The functional role of this phenomenon remains unknown. Recently, selective inhibition of gene expression in the brain using antisense oligodeoxynucleotides became possible. Here, we report that bilateral administration of an antisense oligo against c-fos in the nucleus accumbens blocks cocaine induced locomotor stimulation, without affecting spontaneous exploratory activity. A control sense oligo was inactive. This finding suggests a role for c-fos in mediating psychostimulant effects of cocaine.

PMID: 8319761, UI: 93307410

Neurosci Lett 1996 Dec 20;220(3):155-8

Selective blockade of peripheral delta opioid agonist induced antinociception by intrathecal administration of delta receptor antisense oligodeoxynucleotide.

Bilsky EJ, Wang T, Lai J, Porreca F

Department of Pharmacology, University of Arizona College of Medicine, Tucson 85724, USA.

Previous studies have shown that intrathecal (i.t.) administration of antisense, but not mismatch, oligodeoxynucleotides (ODNs) to the cloned delta opioid receptor (DOR) can inhibit the antinociceptive actions of i.t. delta (delta), but not mu (mu) or kappa (kappa), opioid agonists. As a major portion of spinal opioid receptors are localized on the central terminals of the small afferent fibers, we hypothesized that the effects of antisense ODNs given i.t. might be the result of actions at the level of the cell body in the dorsal root ganglion (DRG). This possibility was investigated by assessing the antinociceptive actions of an i.t. or intrapaw (ipaw) administered mu (morphine), delta ([D-Ala2, Glu4]deltorphin) or kappa (CI977) opioid agonist in rats treated with i.t. saline or antisense or mismatch ODNs to the DOR (12.5 micrograms, twice-daily for 3 days). The opioid agonists produced significant antinociception in the 5% formalin-flinch test following either i.t. or ipaw administration. DOR antisense ODN treatment blocked the antinociceptive actions of both i.t. or ipaw [D-Ala2, Glu4]deltorphin without affecting the antinociceptive actions of i.t. or ipaw morphine or CI977. Radioligand binding studies with [3H]naltrindole (NTI), a delta selective antagonist, indicated an approximate 50% decrease in delta opioid receptors in the lumbar spinal cord following i.t. DOR antisense, but not mismatch, ODN treatment. DOR antisense or mismatch ODN treatment did not affect nu or kappa radioligand binding in lumbar spinal cord. These data suggest the possibility that peripheral proteins can be targeted with i.t. antisense ODNs providing significant opportunities for the exploration of the physiological and pathological significance of these substances.

PMID: 8994216, UI: 97147311

Development 1998 Apr;125(7):1315-24

Hepatocyte growth factor (HGF) acts as a mesenchyme-derived morphogenic factor during fetal lung development.

Ohmichi H, Koshimizu U, Matsumoto K, Nakamura T

Department of Oncology, Biomedical Research Center, Osaka University Medical School, Suita, Osaka, Japan.

Mesenchymal-epithelial tissue interactions are important for development of various organs, and in many cases, soluble signaling molecules may be involved in this interaction. Hepatocyte growth factor (HGF) is a mesenchyme-derived factor which has mitogenic, motogenic and morphogenic activities on various types of epithelial cells and is considered to be a possible mediator of epithelial-mesenchymal interaction during organogenesis and organ regeneration. In this study, we examined the role of HGF during lung development. In situ hybridization analysis showed HGF and the c-met/HGF receptor gene to be respectively expressed in mesenchyme and epithelium in the developing lung. In organ cultures, exogenously added HGF apparently stimulated branching morphogenesis of the fetal lung. In contrast, HGF translation arrest or neutralization assays resulted in clear inhibition of epithelial branching. These results suggest that HGF is a putative candidate for a mesenchyme-derived morphogen regulating lung organogenesis. We also found that HGF is involved in epithelial branching, in collaboration with fibroblast growth factor (FGF) family molecule(s). In mesenchyme-free culture, HGF alone did not induce epithelial morphogenesis, however, addition of both HGF and acidic FGF (aFGF) or keratinocyte growth factor (KGF), ligands for the KGF receptor, induced epithelial branching more extensively than that was observed in explants treated with aFGF or KGF alone. In addition, the simultaneous inhibition of HGF- and FGF-mediated signaling using neutralizing antibody and antisense oligo-DNA resulted in drastic impairment of epithelial growth and branching. Possible interactions between HGF and FGFs or other growth factors in lung development is given consideration.

PMID: 9477330, UI: 98146395